

Highly Active Antiretroviral Therapy and Incidence of Cancer in Human Immunodeficiency Virus-Infected Adults

International Collaboration on HIV and Cancer

Background: The risk of Kaposi's sarcoma and non-Hodgkin's lymphoma is increased in people infected with the human immunodeficiency virus-1 (HIV). Highly active antiretroviral therapy (HAART) has been widely used by HIV-infected people in North America, Europe, and Australia since about 1997. Acquired immunodeficiency syndrome (AIDS) incidence and mortality rates have fallen markedly in association with the use of HAART, but its impact on the incidence of cancer in HIV-infected people is less clear. **Methods:** Cancer incidence data from 23 prospective studies that included 47 936 HIV-seropositive individuals from North America, Europe, and Australia were collated, checked, and analyzed centrally. Adjusted incidence rates (expressed as number of cancers per 1000 person-years) for Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, cervical cancer, and 20 other cancer types or sites were calculated. Rate ratios were estimated, comparing incidence rates from 1997 through 1999 with rates from 1992 through 1996, after adjustment for study, age, sex, and HIV transmission group. All statistical tests were two-sided. **Results:** For the period from 1992 through 1999, 2702 incident cancers were reported in 138 148 person-years of observation, and more than 90% of them were either Kaposi's sarcoma or non-Hodgkin's lymphoma. The adjusted incidence rate for Kaposi's sarcoma declined from 15.2 in 1992 through 1996 to 4.9 in 1997 through 1999 (rate ratio = 0.32; 99% confidence interval [CI] = 0.26–0.40; based on 1489 and 190 cases, respectively; $P < .0001$). The incidence rates for non-Hodgkin's lymphoma also declined, from 6.2 to 3.6 (rate ratio = 0.58; 99% CI = 0.45–0.74; based on 623 and 134 cases, respectively; $P < .0001$). Among the lymphomas, the rate ratios were 0.42 (99% CI = 0.24–0.75) for cerebral lymphoma, 0.57 (99% CI = 0.39–0.85) for immunoblastic lym-

phoma, and 1.18 (99% CI = 0.48–2.88) for Burkitt's lymphoma (χ^2_2 for heterogeneity = 6.2; $P = .05$). There was no statistically significant change in the incidence rates for Hodgkin's disease (rate ratio = 0.77; 99% CI = 0.32–1.85; based on 38 and 12 cases, respectively; $P = .4$) or for cervical cancer (rate ratio = 1.87; 99% CI = 0.77–4.56; based on 19 and 17 cases, respectively; $P = .07$). The adjusted incidence rate for all other cancers combined was 1.7 in each time period (rate ratio = 0.96; 99% CI = 0.62–1.47; based on 126 and 54 cases, respectively). **Conclusions:** Since the widespread use of HAART, there have been substantial reductions in the incidence Kaposi's sarcoma and non-Hodgkin's lymphoma in HIV-infected people but, so far, no substantial change in the incidence of other cancers. [J Natl Cancer Inst 2000;92:1823–30]

Infection with the human immunodeficiency virus-1 (HIV) is associated with an increased risk of developing certain cancers, particularly Kaposi's sarcoma and non-Hodgkin's lymphoma (1). The International Collaboration on HIV and Cancer was set up in 1998 to bring together, reanalyze, and publish worldwide data on the risk of various specific cancers in HIV-infected

Affiliations of the analysis and writing group: P. Appleby, V. Beral, R. Newton, G. Reeves, Cancer Epidemiology Unit, Imperial Cancer Research Fund (ICRF), Oxford, U.K.; L. Carpenter, Department of Public Health, Oxford University.

Correspondence to: Professor Valerie Beral, Secretariat International Collaboration on HIV and Cancer, ICRF, Cancer Epidemiology Unit, Gibson Bldg., The Radcliffe Infirmary, Woodstock Rd., Oxford OX2 6HE, U.K. (e-mail: hivcancer@icrf.icnet.uk).

See "Notes" following "References" section for the complete list of the members of the International Collaboration on HIV and Cancer, including the steering committee and all collaborators.

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people. Preliminary results were discussed at a meeting of collaborators in Oxford, U.K., in September 1999, and a report giving the details of the studies included and the overall results is being prepared for publication. We describe here trends in the incidence of cancer in HIV-infected adults over time, with special emphasis on changes in incidence in developed countries since the introduction of highly active antiretroviral therapy (HAART).

HAART came into widespread use in North America, Europe, and Australia during late 1996 and early 1997; since then, mortality rates from acquired immunodeficiency syndrome (AIDS) have fallen dramatically in developed countries (2–6). The impact of HAART on cancer incidence rates in HIV-infected people is, however, less clear. Some have speculated that, since HIV-infected people live longer, there is a greater potential for them to develop cancer. In this article, incidence rates of Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, cervical cancer, and other cancers in 48 000 HIV-infected people are compared for the years before and after HAART came into widespread use. Follow-up data from 23 prospective studies in North America, Europe, and Australia are included in this international collaboration.

SUBJECTS AND METHODS

Identification of Studies and Collection of Data

A systematic search was undertaken to identify all prospective studies worldwide that had collected information on cancer incidence in cohorts of 1000 or more HIV-infected subjects, irrespective of whether results on cancer incidence had been published. Potentially eligible studies were identified from review articles, from computer-aided literature searches, and from discussions with colleagues. Investigators from each study thus identified were invited to participate in this collaboration. Individual depersonalized data were sought on each subject's age, sex, mode of infection with HIV, date of infection with HIV (if known), date of entry and exit from the cohort, and, where appropriate, date of diagnosis of cancer and type of cancer diagnosed.

All of the data were checked centrally for consistency and completeness. Inconsistent, implausible, or missing data were checked with principal investigators and, where possible, rectified. After all of the records had been corrected, investigators were given tables and listings of variables to be used in the analysis for final checking.

Twenty-three cohort studies were identified that had followed subjects in North America, Europe, or Australia prospectively for cancer incidence beyond 1996 (4–14), and all contributed to these analyses (see Table 1). The Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) (10) normally includes data on seroconverters from 19 separate cohort studies; however, some of these cohorts had contributed their complete datasets to this collaboration and, to prevent duplication of data, these cohorts were omitted, where appropriate, from the results presented for CASCADE (see details in the footnote of Table 1). For the Adult/Adolescent Spectrum of Disease Project Group (14), confidentiality agreements precluded the contribution of data on individuals; analyses were then performed in parallel with those performed centrally, and data were contributed in tabular form in such a way that they could be combined directly with those from the other studies.

For each cancer reported, additional information was sought on cancer site and morphology. It was beyond the remit of this collaboration to review the basis of each diagnosis of cancer. Kaposi's sarcoma was classified according to tumor morphology, and the other cancers were coded according to the International Classification of Diseases (ICD), 9th revision (15). The malignancies included in these analyses were cancers of the lip (ICD 140), pharynx (ICD 146–149), other oral sites (ICD 141–145), esophagus (ICD 150), stomach (ICD 151), colon (ICD 153), rectum (ICD 154, including anus ICD 154.4), liver (ICD 155), lung (ICD 162), connective and soft tissue (ICD 171), malignant melanoma (ICD 172), cancers of the female breast (ICD 174), uterine cervix (ICD 180), ovary (ICD 183), vulva (ICD 184.1–184.4), prostate (ICD 185), testis (ICD 186), penis and other male genitalia (ICD 187), and eye (ICD 190), non-Hodgkin's lymphoma

(ICD 200 and ICD 202), Hodgkin's disease (ICD 201), multiple myeloma (ICD 203), and leukemia (ICD 204–208).

Statistical Methods

For each cancer, person-years and observed number of events were calculated by use of the PERSON-YEARS computer program (16), with individuals contributing person-years from their date of entry up to the date of diagnosis of the cancer of interest, date of death, or date of last follow-up, whichever occurred first. Date of last follow-up is taken to be the most recent date for which the subject's status could be verified (usually through hospital records) or, in the case of studies based on linkage to cancer registry data, the most recent date for which cancer registration records were deemed to be complete. The observed numbers of events and person-years were then cross-classified according to study (and by center within the study), age at diagnosis (<25, 25–29, 30–34, 35–39, 40–44, 45–49, or ≥50 years), calendar period of diagnosis (from 1977 through 1986, from 1987 through 1991, from 1992 through 1996, or from 1997 through 1999), sex, HIV transmission group (sex between men, blood products, injecting drug user, or heterosexual contact/other and unknown), and, where available, by age at seroconversion (0–24, 25–29, 30–34, or ≥35 years) and by time since seroconversion (1–2, 3–4, 5–6, 7–8, 9–10, 11–12, or ≥13 years).

HIV-infected individuals' risk of progressing to AIDS is strongly determined by the age at which they became infected with HIV and their duration of infection (17). The question, therefore, arises as to whether it is necessary to adjust for age at and time since seroconversion in studies of cancer risk in HIV-infected people. The approach adopted here has been initially to carry out analyses restricted to individuals with known dates of seroconversion and to examine the extent to which adjustment for factors related to the timing of seroconversion to HIV affect the results. The results of these analyses, given below, suggest that, for comparisons of incidence in relatively recent periods, adjustment for attained age is an adequate surrogate for adjustment for age at and time since seroconversion. The main analyses of cancer incidence in the period before and after the widespread use of HAART are, therefore, based on rate ratios for cancer incidence in the time periods 1992 through 1996 versus 1997 through 1999, adjusted for study (and center within the study), attained age, sex, and HIV transmission group. Results are also presented in the form of adjusted cancer incidence rates for each calendar period, and details of the method of calculating these adjusted incidence rates are given elsewhere (17). Tests of heterogeneity or trend in rate ratios are based on likelihood ratio statistics calculated from the appropriate Poisson regression model. All tests are two-sided.

For many analyses, results are presented in the form of plots of adjusted rate ratios. Because of the large number of estimates involved, 99% confidence intervals (CIs) are used. Each rate ratio is plotted as a black square, the area of which is proportional to the amount of statistical information for that particular estimate. The statistical information for a given estimate is defined as the reciprocal of the variance of the log rate ratio and reflects the reliability with which that rate ratio is estimated. The corresponding 99% CIs for each rate ratio are drawn as black lines. Where CIs are so narrow as to be contained entirely within the black box, they are printed as white lines, while CIs that extend beyond the scale of the plot are indicated by dotted lines. Summary rate ratios are plotted in the form of a diamond, the width of which indicates the corresponding CI.

RESULTS

Time Trends in Kaposi's Sarcoma and Non-Hodgkin's Lymphoma in People With Known Dates of Seroconversion

Fig. 1 shows incidence rates for Kaposi's sarcoma (Fig. 1, a) and for non-Hodgkin's lymphoma (Fig. 1, b) adjusted for study, sex, age at seroconversion, time since seroconversion, and HIV transmission group, based on data from the studies with estimated dates of seroconversion (7,8,10). Four time periods were chosen to represent 1) the period before the availability of antiretroviral therapy (from 1977 through 1986), 2) the period during which zidovudine was available and the use of other antiretroviral drugs was infrequent (from 1987 through 1991), 3) the period during which zidovudine was available and the use of other antiretroviral drugs was infrequent (from 1992 through

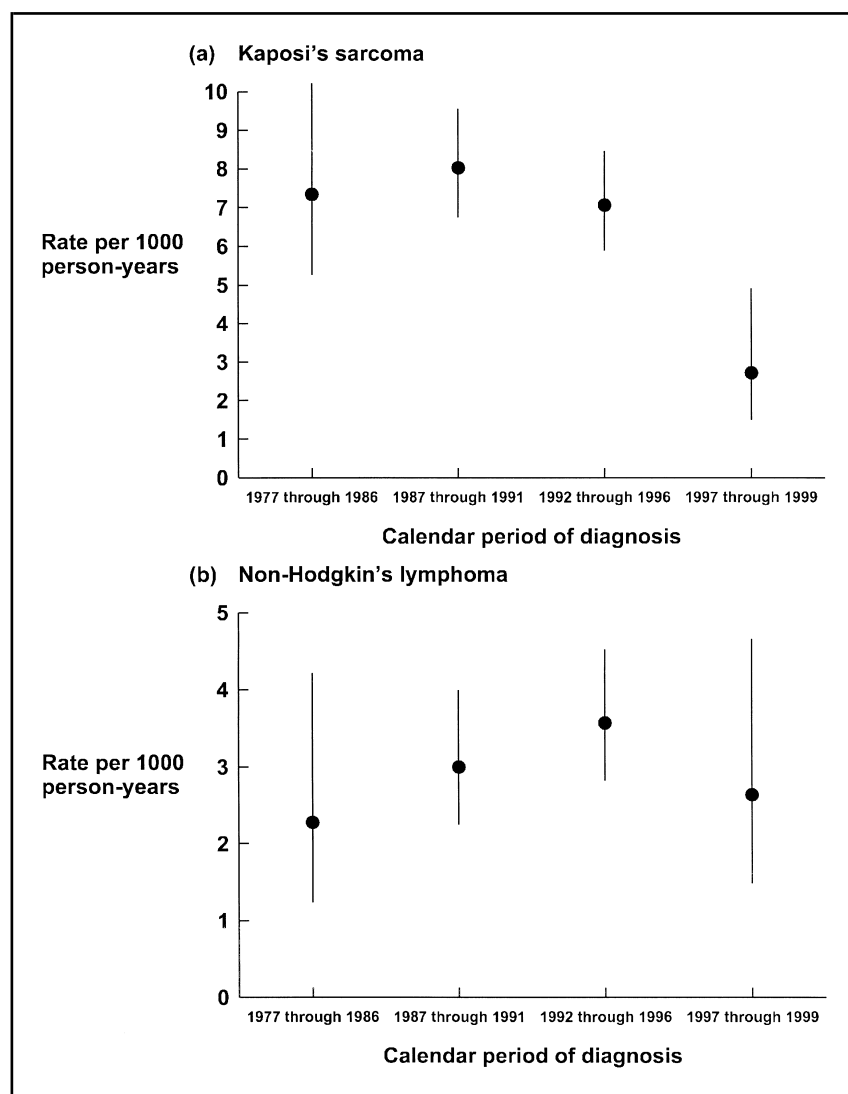


Fig. 1. Incidence rates (99% confidence intervals [CIs]) for Kaposi's sarcoma (**panel a**) and non-Hodgkin's lymphoma (**panel b**), by calendar period, in subjects with known dates of seroconversion to human immunodeficiency virus-1 (HIV). Rates are adjusted for study, age at seroconversion, time since seroconversion, sex, and HIV transmission group (see Table 1 for details).

1996), and 4) the period during which use of HAART was widespread (from 1997 through 1999). It can be seen that, up to the period from 1992 through 1996, the incidence of Kaposi's sarcoma was fairly constant and the incidence of non-Hodgkin's lymphoma was increasing. In 1997 through 1999, however, there was a clear decrease in the incidence of Kaposi's sarcoma compared with previous years ($P < .001$) and a suggestion of a decrease in the incidence of non-Hodgkin's lymphoma, although the decline in the incidence of non-Hodgkin's lymphoma is not statistically significant.

Although it is important to take into account both age at seroconversion and time since seroconversion in examining trends in the incidence of AIDS-associated cancers over long periods of time, adjustment for factors relating to the timing of seroconversion appears to be less relevant when comparing rates over the relatively recent time interval 1992 through 1999. For example, among studies where the dates of seroconversion were known for all subjects, the rate ratio for the incidence of Kaposi's sarcoma in 1997 through 1999 compared with 1992 through 1996, adjusted only for study, attained age, sex, and HIV trans-

mission group, is 0.42 (99% CI = 0.23–0.74), which is very slightly greater than the fully adjusted rate ratio of 0.38 (99% CI = 0.21–0.69). Similarly, the rate ratio for non-Hodgkin's lymphoma in 1997 through 1999 compared with 1992 through 1996, adjusted for study, attained age, sex, and HIV transmission group over the same two time periods, is 0.81 (99% CI = 0.47–1.40), which again is slightly greater than the fully adjusted value of 0.74 (99% CI = 0.42–1.29).

Since comparisons of cancer incidence between relatively recent time periods are not unduly influenced by the timing of seroconversion, the following analyses, which examine the impact of the widespread use of HAART on the incidence of certain cancers among all of the available cohort studies, consider the relative incidence of these cancers in the period from 1997 through 1999 compared with the period from 1992 through 1996, adjusting only for study, attained age, sex, and HIV transmission group.

Cancer Incidence Rates From 1997 Through 1999 Compared With Rates From 1992 Through 1996

Table 1 lists the studies contributing to these analyses and gives the number of subjects, person-years from 1992 through 1996 and from 1997 through 1999, and cases of Kaposi's sarcoma, non-Hodgkin's lymphoma, and other cancers reported in each cohort. Overall, 47 936 HIV-infected individuals were included in the 23 cohorts contributing to these analyses. There were 100 136 person-years of follow-up in 1992 through 1996 and 38 012 person-years in 1997 through 1999. Although all cohorts followed subjects beyond 1996, the last date of follow-up varied across studies, so that the proportion of the total person-years contributed from 1997 through 1999 varied from one study to another. Overall,

1679 incident cases of Kaposi's sarcoma, 757 incident cases of non-Hodgkin's lymphoma, 50 incident cases of Hodgkin's disease, 36 incident cases of cervical cancer, and 180 incident other cancers were reported. In Table 1, it can be seen that all studies contributed information on Kaposi's sarcoma and non-Hodgkin's lymphoma, but some studies did not contribute information on other types of cancer.

Fig. 2 shows data, separately for each study, on the incidence of Kaposi's sarcoma, from 1992 through 1996 and from 1997 through 1999. In each separate study, the adjusted incidence rate for Kaposi's sarcoma from 1997 through 1999 was lower than from 1992 through 1996, and the decline in incidence was statistically significant in many of the individual studies. The ratio of the incidence rates from 1997 through 1999 compared with those from 1992 through 1996 did not vary significantly between cohorts (χ^2 for heterogeneity between studies, 22 df = 26.1; $P = .25$). Overall, the adjusted incidence rate for Kaposi's sarcoma was 15.2 per 1000 person-years from 1992 through 1996 and 4.9 per 1000 person-years from 1997 through 1999, and the overall rate ratio was 0.32 (99% CI = 0.26–0.40;

Table 1. Details of studies contributing to these analyses

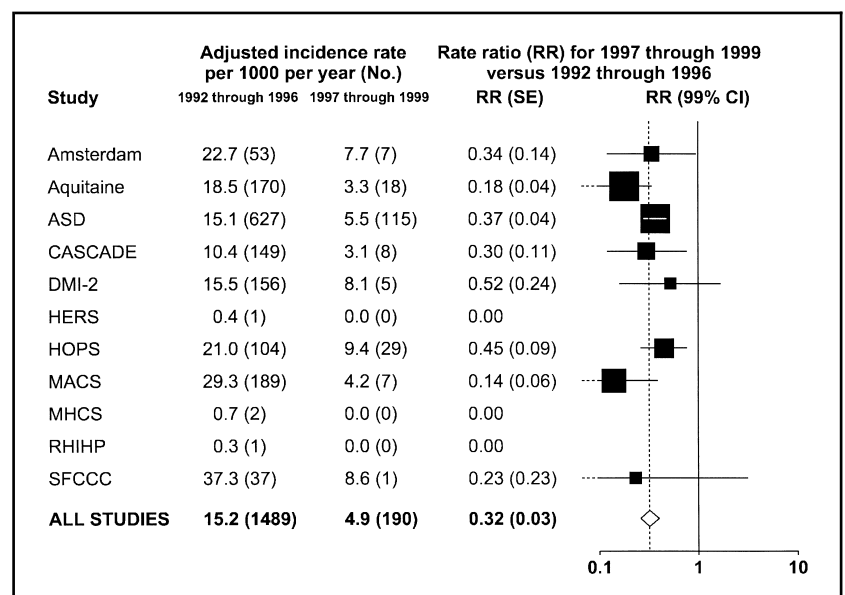
Study name (reference No.)	Country	Total No. of human immunodeficiency virus-positive subjects in the cohort	Person-years		No. of cancers diagnosed from 1992 through 1999				
			1992 through 1996	1997 through 1999	Kaposi's sarcoma	Non-Hodgkin's lymphoma	Hodgkin's disease	Cervical cancer	Other cancers
Cohort studies restricted to subjects with known dates of seroconversion									
CASCADE Collaboration* (CASCADE) (10)	10 countries*	5133	14 539	2676	157	63	N/A†	N/A†	N/A†
Multicenter Hemophilia Cohort Study (8)	Austria/Germany/Greece/Switzerland/United States	1361	2851	491	2	18	0	0	3
Registry of HIV-Infected Hemophilia Patients (RHIHP) (8)	Brazil/Canada/Germany/Israel/Spain/Sweden/UK/United States	1571	3589	736	1	17	2	0	7
San Francisco City Clinic Cohort (SFCCC) (7)	United States	686	1030	142	38	14	N/A†	‡	N/A†
Other cohort studies									
Adult/Adolescent Spectrum of Disease (ASD) (14)	United States	19 684	41 360	21 046	742	317	19	27	102
Amsterdam Cohort Studies (Amsterdam) (11)	The Netherlands	1076	2480	921	60	20	2	0	4
Aquitaine Cohort (Aquitaine) (12)	France	5518	10 017	5052	188	70	17	N/A†	N/A†
DMI-2 Seroprevalence Cohort (DMI-2) (9)	France	4629	10 164	574	161	87	5	3	15
HIV Epidemiology Research Study (HERS) (13)	United States	885	2289	1376	1	8	0	5	8
HIV Outpatients Study (HOPS) (5)	United States	4639	5084	3223	133	49	3	1	18
Multicenter AIDS Cohort Study (MACS) (6)	United States	2754	6731	1774	196	94	2	‡	23
Total		47 936	100 136	38 012	1679	757	50	36	180

*The CASCADE collaboration (Concerted Action on SeroConversion to AIDS and Death in Europe) includes people with known dates of seroconversion from 19 cohort studies, 13 of which are included here: SEROCO (France); German Cohort; Italian Seroconverter Study; Valencia Haemophilia Cohort (Spain); Edinburgh Hospital Cohort (Scotland); Madrid Cohort (Spain); Copenhagen Cohort (Denmark); Oslo Cohort (Norway); Ulleval Hospital Cohort (Norway); UK Register of Seroconverters; Swiss HIV Cohort; Sydney AIDS Prospective Study (Australia); and Sydney Primary HIV Infection Cohort (Australia). Data from the six other collaborating centers either are shown separately (Amsterdam and Aquitaine cohorts) or included in the Registry of HIV-infected Hemophilia patients (the Greek Haemophilia Study and the Royal Free Haemophilia Cohort) or were excluded because they did not include follow-up beyond 1996 (Valencia IDU cohort).

N/A = not available.

‡No cases of cervical cancer are possible, since the cohorts include males only.

Fig. 2. Incidence rates for Kaposi's sarcoma in 1992 through 1996 and in 1997 through 1999 and rate ratios (RRs) of incidence rates in 1992 through 1996 compared with 1997 through 1999, by study. Rates and RRs (displayed with standard errors [SEs] and 99% confidence intervals [CIs]) are adjusted for age, sex, human immunodeficiency virus-1 transmission group, and, within CASCADE, by study. See Table 1 for details of the studies and explanation of the abbreviations. The position of the **square** indicates the RR, and the area of the square is proportional to the amount of statistical information (variance of the logarithm of the RR). The **length of the line** indicates 99% CI; CIs that extend beyond the scale of the plot are indicated by **dotted lines**. Where CIs are so narrow as to be contained entirely within the **black box**, they are printed as **white lines**. **Diamonds** indicate 99% CI for all studies combined. The **vertical broken line** indicates the RR for all studies combined.



$P<.0001$). The rate ratio was similar when analyses were restricted to homosexual men (rate ratio = 0.31; 99% CI = 0.25–0.39).

Fig. 3 shows data, separately for each cohort study, on the incidence of non-Hodgkin's lymphoma from 1992 through 1996 and from 1997 through 1999. In all studies but one, the adjusted incidence rate for non-Hodgkin's lymphoma was lower from 1997 through 1999 than from 1992 through 1996, and the rate ratios did not vary significantly between cohorts (χ^2 for heterogeneity between cohort, 22 *df* = 22.2; P = .45). Although the reduction in incidence reached statistical significance in two studies only, the rate ratio for all studies combined showed a highly significant reduction in incidence from 1997 through 1999 compared with 1992 through 1996 (rate ratio = 0.58; 99% CI = 0.45–0.74; $P<.0001$). The overall adjusted incidence of non-Hodgkin's lymphoma per 1000 person-years in this population was 6.2 from 1992 through 1996 and 3.6 from 1997 through 1999.

Information on morphologic type and/or anatomic site of the tumor was available for 501 (66%) of the 757 subjects with non-Hodgkin's lymphoma. Adjusted incidence rates from 1992 through 1996 and from 1997 through 1999 are shown in Fig. 4 separately for cerebral, immunoblastic, and Burkitt's lymphomas. There was some evidence of variation between the three lymphoma types in the change in incidence between the two time periods (χ^2_2 for heterogeneity = 6.2; P = .05). The rate ratios were 0.42 (99% CI = 0.24–0.75) for cerebral lymphoma, 0.57 (99% CI = 0.39–0.85) for immunoblastic lymphoma, and 1.18 (99% CI = 0.48–2.88) for Burkitt's lymphoma. Although

the number of subjects with Burkitt's lymphoma was small, there was no evidence that the incidence rate changed between the two time periods.

Fig. 5 shows results from all studies combined, for Kaposi's sarcoma, for non-Hodgkin's lymphoma, for Hodgkin's disease, for cervical cancer, and for other cancers. There were too few cases of any specific cancer, other than Kaposi's sarcoma and non-Hodgkin's lymphoma, to show results separately by study. There were a total of 50 cases of Hodgkin's disease, and the rate ratio for incidence rates in 1997 through 1999 compared with 1992 through 1996 was 0.77 (99% CI = 0.32–1.85; P = .44). There were a total of 36 cases of cancer of the uterine cervix, and the corresponding rate ratio was 1.87 (99% CI = 0.77–4.56; P = .07). For the other 20 specific cancer types or sites, no significant change in cancer incidence was seen when each type of cancer was examined separately, but the numbers were small and CIs for rate ratios were wide. For example, 12 cancers of the anus were reported from 1992 through 1996 and six from 1997 through 1999 (rate ratio = 1.50; 99% CI = 0.39–5.71; P = .44). Taking all other cancers together, the adjusted incidence rate was 1.7 per 1000 person-years from 1997 through 1999 (126 cases) and 1.7 per 1000 person-years from 1992 through 1996 (54 cases) (rate ratio = 0.96; 99% CI = 0.62–1.47; P = .80).

There was evidence of substantial heterogeneity between the rate ratios for the three AIDS-defining cancers, i.e., Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer (χ^2_2 for heterogeneity = 40.4; $P<.0001$). The decline in incidence over the two time periods was greatest for Kaposi's sarcoma.

Sensitivity analyses were performed to investigate the possi-

Fig. 3. Incidence rates for non-Hodgkin's lymphoma in 1992 through 1996 and in 1997 through 1999 and rate ratios (RRs) of incidence rates in 1992 through 1996 compared with 1997 through 1999, by study. Rates and RRs (displayed with standard errors [SEs] and 99% confidence intervals [CIs]) are adjusted for age, sex, human immunodeficiency virus transmission group, and, within CASCADE, by study. See Table 1 for details of the studies and explanation of the abbreviations. The position of the **square** indicates the RR, and the area of the square is proportional to the amount of statistical information (variance of the logarithm of the RR). The **length of the line** indicates 99% CI; CIs that extend beyond the scale of the plot are indicated by **dotted lines**. **Diamond** indicates 99% CI for all studies combined. The **vertical broken line** indicates the RR for all studies combined.

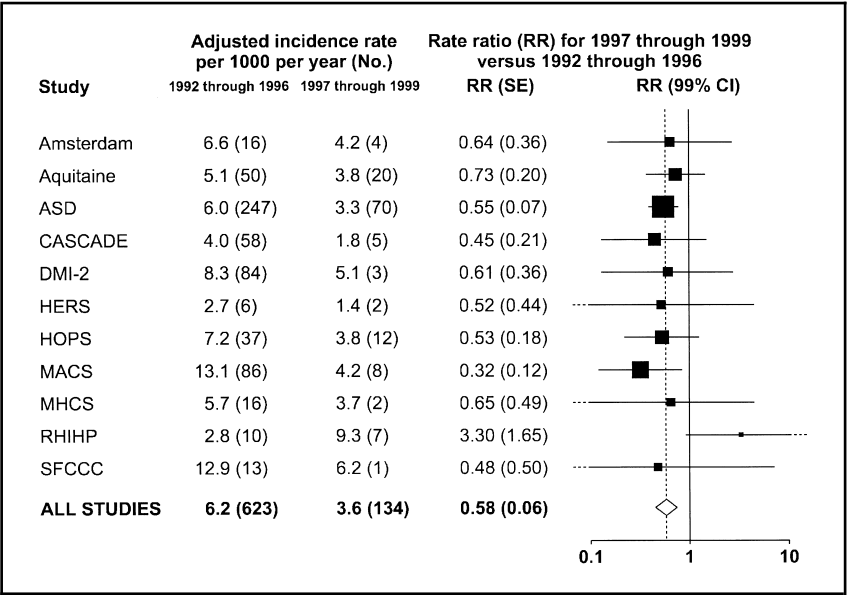


Fig. 4. Incidence rates of certain types of non-Hodgkin's lymphoma in 1992 through 1996 and in 1997 through 1999 and rate ratios (RRs) of incidence rates in 1992 through 1996 compared with 1997 through 1999. RRs (displayed with standard errors [SEs] and 99% confidence intervals [CIs]) are adjusted for age, sex, human immunodeficiency virus-1 transmission group, and study. Each point is based on aggregated data from all studies. Position of the **black squares** represent RRs in proportion to the amount of statistical information (the area of the square represents variance of the logarithm of the RR). The **length of the line** indicates 99% CI.

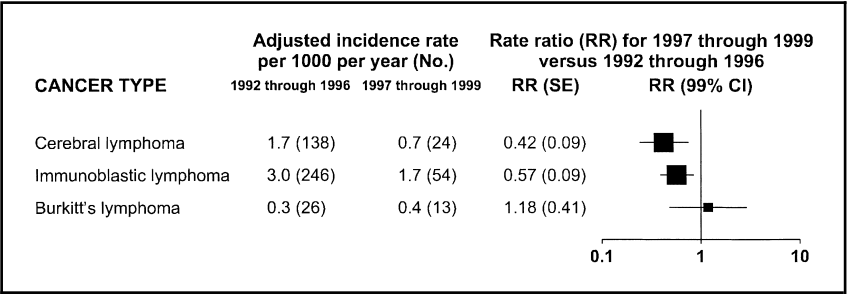
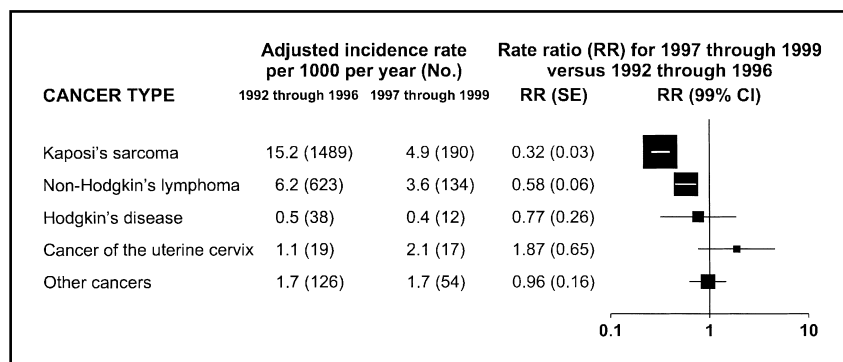


Fig. 5. Cancer incidence rates in human immunodeficiency virus-1 (HIV)-infected adults in 1997 through 1999 compared with 1992 through 1996. Rate ratios (RRs) (displayed with standard errors [SEs] and 99% confidence intervals [CIs]) are adjusted for study, age, sex, and HIV transmission group. Where CIs are so narrow as to be contained entirely within the **black box**, they are printed as **white lines**. Rates and RRs for cancer of the uterine cervix are restricted to females. See the "Subjects and Methods" section for details of the specific cancers included as "other cancers," and see Figs. 2–4 for explanation of format of the plot.



bility that the changes in cancer incidence between the two time periods might be due to changes in the definition of AIDS (which occurred in 1993), the underascertainment of cancer after people developed AIDS, or the underreporting of cancer in recent years. Because data on individuals were not centrally available for the Adult Spectrum of Diseases Project, sensitivity analyses do not include this study. First, to assess the influence of changes in diagnostic criteria in 1993 and the possible incomplete recording of cancers in 1999, analyses were restricted to a more limited time period, i.e., the years 1993 through 1996 and 1997 through 1998. This restriction, however, made little difference to the results (the rate ratio for the period after the widespread use of HAART compared with the earlier period changed from 0.32 to 0.28 for Kaposi's sarcoma and from 0.58 to 0.59 for non-Hodgkin's lymphoma). The effect of potential underascertainment of cancers following a diagnosis of AIDS on the main results was also assessed by restricting follow-up to the period up to a diagnosis of AIDS. The rate ratios for analyses in which the periods of observation were restricted to those before AIDS diagnosis were 0.25 for Kaposi's sarcoma and 0.74 for non-Hodgkin's lymphoma as compared with the overall rate ratios of 0.32 and 0.58, respectively.

DISCUSSION

The results from this collaborative reanalysis of cancer incidence in almost 48 000 HIV-infected adults from 23 cohort studies in developed countries show clear reductions in the incidence of Kaposi's sarcoma and of non-Hodgkin's lymphoma in 1997 through 1999 compared with 1992 through 1996 ($P < .0001$ for each cancer). By contrast, there has been no significant change in the incidence of 22 other cancer types or sites, including Hodgkin's disease, cervical cancer, and anal cancer, each of which has been thought to be increased in HIV-infected people (1). The majority of subjects in these cohorts were using HAART by early 1997 (5,6,10,12,14). Three of these studies together, namely, the Adult Spectrum of Diseases (14), CASCADE (18), and the HIV Outpatients Study (5), contributed 70% of the person-years of observation after 1996; for these studies, the prevalence of use of HAART was approximately 60%, 50%, and 80%, respectively.

This collaborative reanalysis includes, as far as can be ascertained, more than 80% of the person-years of observation available at present from cohort studies in developed countries that permit estimation of cancer incidence rates in HIV-infected adults since the introduction of HAART. Only one large study, the Swiss HIV cohort (19) could not contribute all of its data for these analyses. Although that cohort contributed 1087 person-

years of observation to this collaboration via its contribution of seroconverters to CASCADE, further results based on 18 498 person-years of observation have been published, and these also showed a reduction in cancer incidence in the period June 1997 through June 1998 compared with 1992 through 1994 for Kaposi's sarcoma (rate ratio = 0.08; 95% CI = 0.03–0.22) and for non-Hodgkin's lymphoma (rate ratio = 0.61; 95% CI = 0.30–1.29) (19). Combining these published estimates with the results shown in Fig. 5 makes little difference to the overall findings, the re-estimated relative risks being 0.31 (99% CI = 0.26–0.38) for Kaposi's sarcoma and 0.58 (99% CI = 0.45–0.74) for non-Hodgkin's lymphoma. Cohort studies that included fewer than 1000 HIV-infected persons would contribute relatively small numbers of person-years to the total 138 148 person-years analyzed here, and so their exclusion from this collaboration would not be expected to have materially affected the results.

The rate ratios shown in Figs. 2–5 are unlikely to be biased by differences in the characteristics of the cohorts. All analyses are adjusted for study, as well as by age, sex, and HIV transmission group; therefore, any differences in underlying cancer incidence rates between the populations should have been taken into account. Moreover, there is no evidence of significant variation in the rate ratios between the individual studies contributing to these analyses. The results did not vary markedly according to HIV transmission group or region of residence. Even though the main results have not been adjusted for factors related to the timing of HIV seroconversion, our analyses of subjects with known dates of seroconversion indicate that such adjustments would have negligible effects on the rate ratios presented here. Indeed, analyses restricted to subjects with known dates of seroconversion suggest that failure to adjust for these factors would, if anything, lead to a slight underestimation of any decline in cancer incidence between 1992 through 1996 and 1997 through 1999. The results of sensitivity analyses also suggest that the main findings are unlikely to be materially altered by changes in the diagnostic criteria for AIDS, by the possibility that cancer is less completely reported after AIDS is diagnosed, or by the possible underascertainment of cancer in the later years of follow-up. Because not all members of these cohorts received HAART after 1997, and some may have already been receiving it by 1996, the results presented here would tend to underestimate the effect of HAART on cancer incidence.

AIDS-defining cancers (Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer) contribute more than 90% of the 2702 cancers reported in these cohorts, and these cancers tend to be the ones showing substantial reductions in incidence since the introduction of HAART. However, there is evidence of hetero-

geneity between the AIDS-defining cancers in the relative decline in incidence over time—Kaposi's sarcoma shows the greatest decline (rate ratio = 0.32)—followed by cerebral lymphoma (rate ratio = 0.42) and immunoblastic lymphoma (rate ratio = 0.57). Burkitt's lymphoma (rate ratio = 1.18) and cervical cancer (rate ratio = 1.87) show no evidence of a decline, although the numbers of each of these cancers are small. In HIV-infected people, Kaposi's sarcoma and cerebral lymphoma occur, on average, at considerably lower CD4 levels than does Burkitt's lymphoma or cervical cancer. For example, in the Adult/Adolescent Spectrum of Diseases Project, the median CD4 count (cells/ μ L) at cancer diagnosis was 41 for Kaposi's sarcoma, 12 for cerebral lymphoma, 72 for immunoblastic lymphoma, 120 for Burkitt's lymphoma, and 206 for cervical cancer [(14); Jones J: unpublished data]. These observations suggest that the malignancies that occur at low CD4 levels in HIV-infected individuals are also those that have shown the greatest decline in incidence since the widespread use of HAART, providing indirect support for the view that immunosuppression may be a key factor in the development of these tumors in HIV-infected subjects.

Cervical cancer and other anogenital cancers are caused by infection with certain types of human papillomaviruses, and the role of HIV infection and its associated immunosuppression in inducing these cancers is unclear (1). Both cervical and anal cancers can be detected at an early stage, and it is unknown whether there has been a change in screening practices for these cancers in HIV-infected people since the introduction of HAART. This uncertainty, taken together with the small number of either type of cancer occurring in these cohorts (36 cervical and 18 anal cancers), means that the only conclusion that can be drawn at this stage is that neither cancer appears to be extremely common in HIV-infected subjects. Longer follow-up and substantially larger studies would be required to evaluate the effects of HAART on the incidence of these human papillomavirus-associated cancers.

For the other non-AIDS-defining cancers examined, no significant changes in cancer incidence were found, either when the cancers were examined separately or when they were combined together. However, when most of the available evidence worldwide is combined, as has been done here, the total number of non-AIDS-defining cancers and the number of individuals with any particular type of cancer is still not large. In addition, HAART has been in use for a few years only, and the possibility that such therapy may affect the incidence of certain cancers in the long-term cannot be excluded. It will, therefore, be important to continue to monitor cancer incidence in HIV-infected people in the future.

In conclusion, the sharp decline in the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma and the lack of an increase in other malignancies since the widespread use of HAART are reassuring for HIV-infected subjects and do not, at this stage, support the view that cancer incidence rates might increase as HIV-infected people survive longer.

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NOTES

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The Secretariat of the International Collaboration on HIV and Cancer: P. Appleby, V. Beral, L. Carpenter, D. Casabonne, H. Deo, N. Langston, R. Newton, and G. Reeves.

The Steering Committee of the International Collaboration on HIV and Cancer: H. Jaffe (chairman), E. Feigal, M. Melbye, S. Melnick, and F. Sitas.

Participating studies/institutions (investigators): Adult/Adolescent Spectrum of HIV Disease (H. Jaffe, J. Jones); AIDS–Cancer Match Study (R. Biggar, J. Goedert); Amsterdam HIV Cohort (R. A. Coutinho, M. Prins, B. van Benthem, L. van Asten); Aquitaine Cohort (F. Dabis, S. Lawson-Ayayi); Cancer and AIDS

Record Linkage Study (L. Dal Maso, S. Franceschi); CASCADE (Aquitaine cohort: F. Dabis, C. Marimoutou; SEROCO cohort: L. Meyer, F. Boufassa; German cohort: O. Hamouda; Italian Seroconversion Study: P. Pezzotti, G. Rezza; Valencia haemophilia cohort: J. Lorenzo; Greek Haemophilia cohort: G. Touloumi, A. Hatzakis, A. Karafoulidou, O. Katsarou; Edinburgh Hospital cohort: R. Brett; Madrid cohort: J. Del Amo, J. del Romero; Amsterdam Cohort Study among drug users: M. Prins, R. Coutinho; Amsterdam Cohort Study on homosexual men: B. van Benthem, R. Coutinho; Copenhagen cohort: O. Kirk, C. Pedersen; Valencia IDU cohort: I. Hernández Aguado, S. Pérez-Hoyos; Oslo and Ullevaal Hospital cohorts: A. Eskild, J. Bruun, M. Sannes; Royal Free haemophilia cohort: C. Sabin, C. Lee; U.K.; Register of HIV Seroconverters: A. Johnson, A. Phillips, A. Babiker, J. Darbyshire, N. Gill, K. Porter; Swiss HIV cohort: M. Egger, P. Francioli, M. Rickenbach; Sydney AIDS Prospective Study: D. Cooper, J. Kaldor; Sydney Primary HIV Infection cohort: D. Cooper, J. Kaldor, J. Vizzard; and MRC Biostatistics Unit, Cambridge: N. Day, D. De Angelis; *CASCADE Steering Committee*: V. Beral, R. A. Coutinho, J. Darbyshire, N. Gill, C. Lee, L. Meyer, G. Rezza); DMI-2 Seroprevalence Cohort (M. P. Carrieri, P. Dellamonica, C. Pradier, D. Serraino); HIV Epidemiology Research Study (A. Duerr, L. Gardner, S. D. Holmberg, D. Jamieson, A. Levine, R. Phelps on behalf of the HER Study Group); HIV Outpatients Study (HOPS) Investigators (S. D. Holmberg, A. Moorman, T. Tong, K. Wood, and the HOPS investigators); Johannesburg Cancer Case-Control Studies (H. Carrara, R. E. Pacella-Norman, F. Sitas); Multicenter AIDS Cohort Study (R. Detels, L. Jacobson, J. Margolick, J. P. Phair, C. Rinaldo); Multicenter Hemophilia Cohort Study (J. Goedert, C. Rabkin); New South Wales AIDS-Cancer Record Linkage Study (A. Grulich, J. Kaldor, M. Law); Registry of HIV-Infected Hemophilia Patients (J. J. Goedert, C. Rabkin); Rwandan Cancer Case-Control Study (V. Beral, A. Grulich, R. Newton, P. J. Ngilimana, D. M. Parkin); San Francisco City Clinic Cohort (S. P. Buchbinder, N. Hessel, E. Vittinghoff); Swiss HIV Cohort Study (M. Egger, P. Francioli, M. Rickenbach); and Ugandan Cancer Case-Control Study (V. Beral, L. Carpenter, E. Mbidde, R. Newton, D. M. Parkin, J. Ziegler).

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